**Annals of Clinical and Analytical Medicine**
*Original Research*

# Evaluation of the effects of three different postoperative analgesic methods on thiol/disulphide homeostasis

Postoperative analgesia and thiol/disulphide balance

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**Abstract**

Aim: Trauma increases oxidative stress at the cellular level, with thiol/disulfide homeostasis serving as a direct indicator of the cell's oxidative state. Oxidative stress leads to a decrease in thiol levels and an increase in disulfide levels. This study aimed to investigate the correlation between total thiol, native thiol/disulfide levels, and pain scores using three different analgesic methods.

Material and Methods: Sixty patients with an ASA score of I–III undergoing proximal femoral nail (PFN) surgery under hypobaric spinal anesthesia were randomly divided into three groups. Group I received IV patient-controlled analgesia (PCA), Group II received epidural PCA, and Group III underwent USG-guided femoral–sciatic nerve block. Postoperative VAS scores at 3, 6, and 24 hours were recorded. Paracetamol (1g IV) was given when VAS exceeded 3. Total thiol, native thiol, and disulfide levels were measured preoperatively, 30 minutes perioperatively, and at 3, 6, and 24 hours postoperatively.

Results: Hypobaric spinal anesthesia increased thiol levels and decreased disulfide levels. In all groups, total and native thiol levels increased, while disulfide levels decreased postoperatively. No significant differences were noted among groups regarding thiol and disulfide levels. Similarly, VAS scores were comparable across all groups.

Discussion: Spinal anesthesia effectively reduces oxidative stress. The three analgesic methods (IV PCA, epidural PCA, and femoral–sciatic nerve block) showed no significant differences in their effects on basal thiol, native thiol, or disulfide levels. All methods provided comparable analgesia and oxidative stress control following PFN surgery.

**Keywords**

Thiol-Disulfide, Epidural, Spinal, Proximal Femoral Nail, Patient-Controlled Analgesia

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## Introduction

Elderly patients admitted to the hospital with a hip fracture have several characteristics that complicate the management of anesthesia and analgesia. These characteristics, including low cardiac/respiratory reserves, use of multiple drugs that can interact with anesthetic and analgesic agents, and sensitivity to opioids, increase the morbidity and mortality in such patients. Cardiovascular and cerebrovascular diseases, which are common in older individuals, cause increased oxidative stress [1]. Moreover, trauma, surgery, and pain lead to the activation of several neuroendocrine pathways, subsequently resulting in the exacerbation of stress responses.

Effective analgesia initiated in the pre-operative period often requires the selection of individualized agents and methods. Subjective pain scoring systems, such as the visual analog scale (VAS), are used for the personalized evaluation of pain control. However, stress markers must be used to quantitatively evaluate the oxidative state caused by surgical stress and pain. The thiol/disulfide balance is a direct indicator of the oxidative state and damage within a cell. A decrease in the total thiol and native thiol levels in the native thiol/disulfide ratio and an increase in the disulfide levels are considered an imbalance in favor of oxidative stress [2].

In the present study, we aimed to investigate the most effective method for pain control by examining the correlation of different post-operative analgesia methods with the thiol/disulfide balance in patients operated under spinal anesthesia for a proximal femoral fracture.

## Material and Methods

The present study was conducted between November 2016 and March 2018 at a tertiary referral hospital. The study included 60 patients aged >65 years who were scheduled to undergo surgery with a proximal femoral nail (PFN) at the Orthopaedics and Traumatology Clinic for a proximal femoral fracture and who had an American Society of Anaesthesiologists (ASA) score of I–III, and who agreed to participate in the study.

Before the surgery, patients with the following conditions were excluded from the study: possible need for post-operative intensive care, ASA score of IV, continuous pain medication used due to chronic pain, allergy to local anesthetics, refusal to have regional anesthesia performed, lower extremity neurological dysfunction, injection site infection, and coagulopathy.

In addition to obtaining informed consent, the relatives of the patients were provided training regarding the 10-cm VAS ruler. The patients included in the study were randomly divided into three groups using the closed-envelope method.

Group I: The patients in this group received intravenous (IV) patient-controlled analgesia (PCA) for postoperative analgesia following spinal anesthesia (20 mg/h infusion with tramadol, 20 mg IV bolus dose, and 20 min lockout time).

Group II: The patients in this group were administered a combined spinal–epidural set and received epidural PCA for postoperative analgesia (0.125% bupivacaine 4 mL/h infusion, 4 mL bolus dose, and 15 min lockout time).

Group III: The patients in this group received an ultrasound (USG)-guided combined femoral–sciatic nerve block for postoperative analgesia following spinal anesthesia (20 mL of 0.25% bupivacaine solution in each area).

The patients were taken to the operating room, and thereafter, they first underwent routine electrocardiography (ECG) and non-invasive blood pressure and peripheral oxygen saturation (SpO2) monitoring, after which the radial artery was catheterized, and a 2-mL blood sample was collected into a plain gel biochemistry tube for pre-operative (T0) thiol/disulfide level measurements.

Peak heart rate as well as invasive systolic, diastolic, and mean blood pressure values of the patients were recorded when they were taken to the operating room (T0) and every 15 minutes thereafter.

After the patients were positioned in an appropriate lateral decubitus position with their fractured leg to be operated on top, the patients in all the groups were administered spinal anesthesia with mL of hypobaric solution (3 mL was drawn into the injector from the 4 mL hypobaric solution prepared with 10 mg 0.5% bupivacaine, 40 µg fentanyl and 1.2 mL distilled water) using a combined spinal–epidural set (18 G epidural needle, 27 G spinal needle, Egemen, Turkey) in Group II and a Quincke spinal needle (25 G, Egemen, Turkey) in Groups I and III. At 30 min after the application of spinal anesthesia, blood samples were collected from all the patients for thiol/disulfide value (T1) measurements. At the end of the surgery, USG (Esaote MyLab TM 30Gold Cardiovascular USG, Genoa)-guided combined femoral–sciatic nerve block (100-mm 21G, Locoplex, Vygon, France) was performed in Group III.

At 3(T2), 6 (T3), and 24 (T4) h post-operatively, the pain levels of the patients were evaluated using VAS, blood samples were obtained for thiol/disulfide level measurement and the peak heart rate and non-invasive systolic, diastolic and mean blood pressure values were recorded. During the post-operative follow-up, 1 g of paracetamol was intravenously administered as a rescue analgesic in patients with a VAS score of >3. The number of bolus doses administered with PCA and the need for additional analgesics were recorded.

### *Power Analysis*

Power analysis was performed using the G*Power software based on a pilot study conducted with 5 patients from each group. When the effect size d and SD were considered 0.436 and 2.4, respectively, for the decrease in the number of native thiol levels from T0 to T1, the number of samples for a power of 0.80 and of 0.05 was determined as a minimum value of n=19 for each subgroup. Considering the possibility of data loss during follow-ups, it was decided to include 20 patients per group in the study.

### *Statistical Analysis*

IBM SPSS Statistics 22.0 (IBM SPSS, Turkey) was used for statistical analysis of the study results. For evaluating the study data, the conformity of the parameters to normal distribution was evaluated using the Shapiro–Wilks test. In addition to descriptive statistical methods (mean, standard deviation, and frequency), one-way ANOVA was used to compare the quantitative data for intergroup comparisons of normally distributed parameters, whereas Tukey's honestly significant difference test was used to identify the group that caused the difference. The Kruskal–Wallis test was used for intergroup comparisons of parameters not showing normal distribution,

whereas the Mann–Whitney U test was used to identify the group that caused the difference. Paired sample t-test was used for intragroup comparisons of quantitative data showing normal distribution, whereas the Wilcoxon signed-rank test was used for intragroup comparisons of the parameters not showing normal distribution. The chi-square and Fisher–Freeman–Halton tests were used for the comparison of qualitative data. A p-value of <0.05 was considered statistically significant.

*Ethical Approval*

This study was approved by the Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital (Date: 2016-09-22, No: 2016/44).

## Results

In the present study, gender, ASA scores, surgical duration, and patient satisfaction were similar in all the groups (p > 0.05) (Table 1). Although there was no significant difference between Groups I and II in terms of age, the mean age of the patients in Group III was higher compared with that of patients in Groups I and II (p1: 0.005; p2: 0.038; p < 0.05).

Although the peak heart rates were similar up to 6h postoperatively in all the groups, it was higher in Group II than in Group I at 6 and 24h post-operatively (Figure 1).

Intergroup comparison (one-way ANOVA p:0.008, p:0.001; p < 0.05).

●When compared with T0 in Groups I, II, and III (paired sample t-test; p < 0.05)

◊ When compared with T0 in Group II (paired sample t-test; p < 0.05).

No significant difference was observed between the groups in terms of mean arterial pressure values (p > 0.05).

No significant difference was observed between the groups in terms of the VAS scores obtained at 3 (T2), 6 (T3), and 24 h (T4) post-operatively (p > 0.05). The need for additional analgesics was similar between the groups (Table 2).

● Intergroup comparison (one-way ANOVA; p:0.037)

When compared with T0 in the groups (paired sample t-test; p<0.05).

In all three groups, the perioperative and post-operative native thiol levels were higher than pre-operative (T0) native thiol levels (p: 0.000; p: 0.000; p1: 0.001, p2–4: 0.000, p < 0.05) (Figure 2).

The native thiol levels at 24 h (T4) postoperatively were significantly higher in the epidural PCA group (Group II) than in the IV PCA group (Group 1) (p: 0.029; Tukey's honestly significant difference test); no significant difference was observed between the other two groups.

The total thiol levels were similar in the three groups at all measurement times (p > 0.05). The perioperative and post-operative total thiol levels were higher than pre-operative total

**Table 1.** Demographic parameters, duration of surgery, and patient satisfaction

| | | Group I | Group II | Group III | Total | p |
|---|---|---|---|---|---|---|
| | | Mean±SD | Mean±SD | Mean±SD | Mean±SD | |
| Age years | | 74.65±4.34 | 75.9±6.1 | 80.3±5.8 | 76.97±5.9 | [1]0.005* |
| Gendern (%) | Male | 10 (50%) | 10 (50%) | 8 (40%) | 28 (46.7%) | [3]0.765 |
| | Female | 10 (50%) | 10 (50%) | 12 (60%) | 32 (53.3%) | |
| ASA n (%) | 2 | 1 (5%) | 4 (20%) | 4 (20%) | 9 (15%) | [4]0.360 |
| | 3 | 19 (95%) | 16 (80%) | 16 (80%) | 51 (85%) | |
| Surgical duration (median) | | 114.7±15.6 (112.5) | 119.3±20.34 (120) | 121.5±14.52 (120) | 118.5±16.96 (120) | [2]0.379 |
| Patient satisfactionn (%) | 4 | 1 (5%) | 4 (20%) | 4 (20%) | 9 (15%) | [4]0.360 |
| | 5 | 19 (95%) | 16 (80%) | 16 (80%) | 51 (85%) | |

[1]One-way ANOVA [2]Kruskal–Wallis Test [3]Chi-square Test [4]Fisher–Freeman–Halton Test
*p < 0.05

**Table 2.** The need for additional analgesics

| | | Group I | Group II | Group III | Total | P |
|---|---|---|---|---|---|---|
| | | Mean±SD | Mean±SD | Mean±SD | Mean±SD | |
| Additional analgesicneed n (%) | No | 19 (95%) | 19 (95%) | 18 (90%) | 56 (93.3%) | 1.000 |
| | Yes | 1 (5%) | 1 (5%) | 2 (10%) | 4 (6.7%) | |

Fisher–Freeman–Halton Test
*p < 0.05

**Table 3.** Changes observed in the disulfide levels from T0 to T1 and T2 in all the groups

| | Disulphide levels(T0–T1 difference) | Disulphide levels (T0–T2difference) |
|---|---|---|
| | Mean±SD (median) | Mean±SD (median) |
| Group I | −4.6±3.69 (−3.55) | −6.86±3.25 (−5.85) |
| Group II | −5.29±3.91 (−6.25) | −8.86±4.97 (−8.63) |
| Group III | −5.44±3.36 (−6.15) | −8.37±3.93 (−9.1) |
| p | 0.642 | 0.317 |

Kruskal–Wallis test

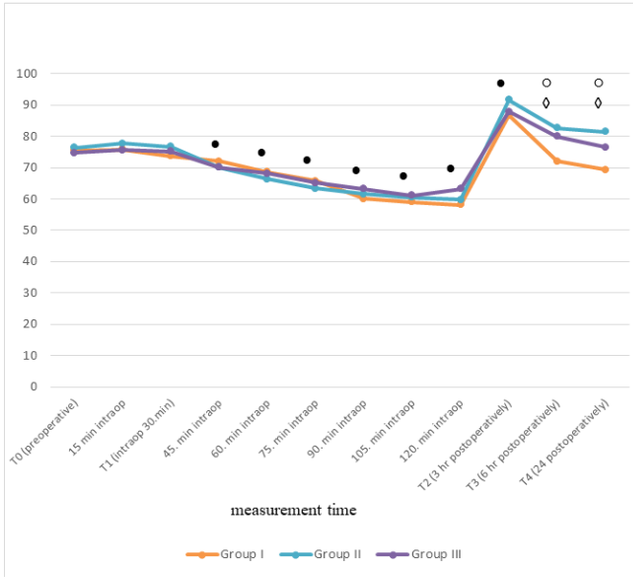


**Figure 1.** Peak heart rate evaluation

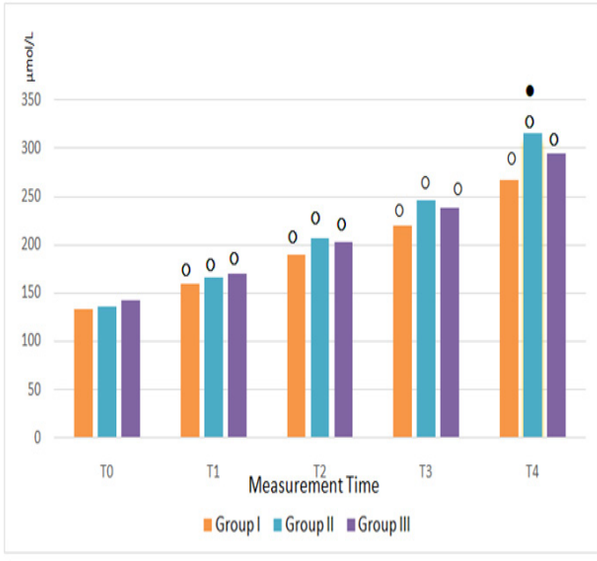


**Figure 2.** Native thiol level evaluation

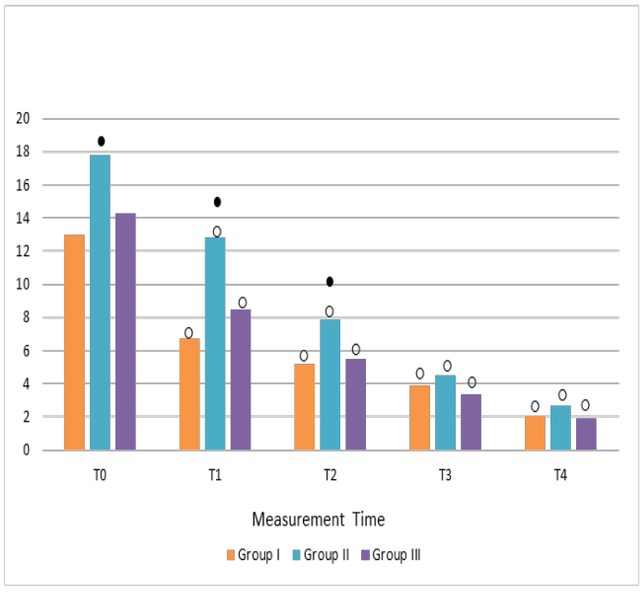


**Figure 3.** Disulphide level evaluation

thiol levels in all three groups (p: 0.000, p: 0.000, p1: 0.009, p2–4: 0.000; p < 0.05).

● Intergroup comparison (Kruskal–Wallis test, p<0.05)

Intragroup comparison according to T0 (‡paired sample t-test). In all three groups, the perioperative and post-operative disulfide levels were lower than the pre-operative levels (p: 0.000, p: 0.000, p: 0.000, p < 0.05) (Figure 3). The preoperative (T0), 30 min perioperative (T1), and 3 h (T2) postoperative disulfide levels were higher in the epidural PCA group (Group II) than in the IV PCA group (Group I) (p: 0.011, p: 0.005, p: 0.009; p < 0.05). The 3h (T2) post-operative disulfide levels were higher in the epidural PCA group (Group II) than in the combined femoral–sciatic nerve block group (Group III) (p: 0.042). No significant difference was observed between the groups in terms of the decrease observed in the disulfide levels from T0 to T1 and T2 (Kruskal–Wallis test, p > 0.05) (Table 3).

## Discussion

The present study was conducted in elderly patients who underwent femoral nail surgery for a proximal femoral fracture, and to the best of our knowledge, this is the first study to evaluate the effects of three different postoperative analgesia methods administered following spinal anesthesia on oxidative stress by measuring the thiol/disulfide balance.

All the patients were operated on under spinal anesthesia, and they were administered IV PCA, epidural PCA, or combined femoral–sciatic nerve block for postoperative analgesia. The present study demonstrated that the application of hypobaric spinal anesthesia resulted in an increase in the thiol levels and a decrease in the disulfide levels, thereby indicating a decrease in oxidative stress. The VAS scores were similar in all the groups, and no difference was observed in the use of additional analgesics. Similar and effective levels of analgesia were ensured in all the patients. The similarity of the thiol/disulfide balance in all three groups demonstrated that there was no difference in the level of oxidative stress caused by pain among IV PCA, epidural PCA, and combined femoral–sciatic nerve block.

In aerobic organisms, free oxygen radicals are released as a result of normal oxygen metabolism. These radicals are highly reactive due to the single electron in their outer shell. Free radicals are continuously produced as a result of normal metabolic processes. The activation of several neuroendocrine, humoral, and cellular pathways in the body due to trauma, inflammation, surgical/emotional stress, and pain leads to an excessive increase in free radical production and consequently causes an increase in oxidative stress. As the body's defense mechanism, antioxidant molecules prevent oxidative damage by forming bonds with reactive oxygen molecules [3-5]. Because reactive oxygen species are highly reactive, with a short half-life and low concentration, different indirect markers, rather than direct measurement, are used to evaluate cellular damage. Thiol, which is an organic compound, is one of the antioxidant molecules that play a crucial role in the body's defense mechanism against reactive oxygen derivatives. When thiol encounters oxidative stress, its sulfhydryl (-SH) group oxidizes to form a disulfide bond and protects protein structures from oxidation. Disulfide bonds can be reduced back to thiol groups.

Owing to this reversible reaction, the oxidative state within a cell can be measured on the basis of the decrease in thiol levels and increase in disulfide levels [6]. Although only the thiol parameter of this balance could be measured using the Ellman method since 1979, the new method developed by Erel and Neşelioğlu allows both separate and cumulative measurement of the native thiol (-SH), dynamic disulfide (-S-S-) and total thiol [(-SH) + (-S-S-)] levels [7]. A decrease in the total thiol and native thiol levels in the native thiol/disulfide ratio and an increase in the disulfide level are considered indicative of oxidative stress [8, 9].

Regional anesthesia/analgesia reduces the stress response to surgery by ensuring both afferent sensory block and efferent sympathetic block [10-12]. Akın et al. investigated the relationship between the anesthesia technique performed in cesarean section and the thiol/disulfide balance and demonstrated that a mother and a newborn who were operated under general anesthesia experienced higher oxidative stress than a mother and a newborn who was operated under spinal anesthesia [13]. In the present study, the decreased disulfide levels and increased native thiol and total thiol levels following spinal anesthesia, which resulted in a shift of thiol/disulfide balance in the direction of thiol, support the argument that spinal anesthesia reduces oxidative stress.

In the postoperative period, pain creates emotional stress and stimulates the autonomic nervous system, thereby triggering the secretion of hormones, such as epinephrine and cortisol as well as inflammatory cytokines [14]. Several studies have reported that epidural analgesia achieved with opioids and/or local anesthetics provides better pain control than intramuscular or IV opioids [15-18]. In addition, local anesthetics administered via the epidural route are considered to exert a stronger effect in suppressing the stress response than opioids because they block both the nociceptive and non-nociceptive pathways [19]. Epidural anesthesia provides support to the cell in the prevention of oxidative damage [20, 21]. In the present study, only native thiol levels measured at post-operative 24 h were higher in the epidural PCA group (Group II) than in the IV PCA group (Group I) ($p: 0.029$; $p < 0.05$); however, the total thiol levels as well as the changes in disulphide levels were similar between the groups.

An alternative to neuraxial blocks is peripheral nerve blocks. Chelly et al. suggested that the post-operative combined femoral–sciatic nerve block provides better analgesia than epidural analgesia and morphine PCA [22]. Davies et al. considered a single-dose femoral–sciatic nerve block as a useful alternative to epidural analgesia [23]. In the present study, three different methods were used for the administration of analgesia in the postoperative period. Effective analgesia was confirmed in all the patients on the basis of the VAS scores and high patient satisfaction. In all the groups, the disulfide levels obtained at 3, 6, and 24 h post-operatively were low (p: 0.000). During the postoperative follow-ups, the decrease in the disulfide levels and increase in the native total thiol levels in all the patients demonstrated that effective analgesia was achieved and that IV PCA, epidural PCA and combined femoral–sciatic nerve block reduced oxidative stress.

### *Limitation*

The present study had some limitations. One of the limitations was that the mean age of the patients in the combined femoral–sciatic nerve block group (Group III) was high, and it has been reported that oxidative stress increases with increasing age [24]. In addition, the present study was conducted with patients having high levels of basal oxidative stress due to the femoral fracture. Concomitant diseases and multiple drug use in geriatric patients may have been manifested with the high basal disulfide levels. Therefore, a comparison was made between the decrease in the disulfide levels obtained with anesthesia/analgesia. No significant difference was observed between the groups in terms of the changes in the disulfide and native total thiol levels.

### *Conclusion*

The present study demonstrated that oxidative stress decreases with hypobaric spinal anesthesia in elderly patients who underwent surgery for a femoral fracture. It was concluded that it is important to provide effective analgesia in the postoperative period for managing oxidative stress, regardless of the selected analgesic method.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and Human Rights Statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.*

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***Conflict of Interest***

*The authors declare that there is no conflict of interest.*

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